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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/484,121	01/13/00	SCHUMANN R	0107-020P/GP

023622
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HM12/0618

EXAMINER	
KAM,C	

ART UNIT	PAPER NUMBER
1653	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/484,121	Applicant(s) SCHUMANN ET AL.	
	Examiner Chih-Min Kam	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2001* .

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-23* is/are pending in the application.

4a) Of the above claim(s) *18-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because non-initialed and/or non-dated alterations have been made to the oath or declaration, e.g., the oath or declaration under postal address for inventor Lamping. See 37 CFR 1.52(c).

Election/Restrictions

Applicant's election of Group I, claims 12-17 in Paper No. 13 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim Objections

1. Claim 12 is objected to because of the use of the term "protein binding lipopolysaccharide (LBP)". Use of the term "lipopolysaccharide binding protein (LBP)" is suggested. The dash lines "- -" before and at the end of the claim should be deleted in all the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 12-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an agent containing murine recombinant LBP as the active component

for treating septicemia, does not reasonably provide enablement for an agent containing LBP from species such as human, rat or rabbit, its variant, mutants or hybrid proteins as the active component for treating septicemia. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 12-17 are drawn to encompass an agent containing LBP from different species such as human (claims 12 and13), murine (claims 12 and 14), rat or rabbit (claims 12 and 15), its variant, mutants (claims 12 and 17) or hybrid proteins (claims 12 and 16) as the active component for treating septicemia. The specification, however, only discloses cursory conclusions (page 1, lines 24-32), without data to support the findings, which states that an agent containing LBP from different species such as human, murine, rat or rabbit, its variant, mutants or hybrid proteins as the active component for treating septicemia. The specification only discloses one LBP (murine LBP) at high doses suppresses the production of TNF-α, suppresses the liver damage induced by LPS and reduces the lethality in a LBP septicemia model (see drawings), however the murine LBP is not representative of all LBPs which might not have the same level of activity as murine LBP due to sequence variations, e.g., rat LBP has 59% sequence homology to rabbit LBP and 66% homology to human LBP (Su et al., J. Immunology 153, 743-752 (1994)). It appears that the function of LBP remains unclear due to conflict results, LBP has been reported to potentiate the host response to LPS, eventually resulting in pathogenic states such as septic shock (Schumann et al., Science 249 (4975) 1429-1431 (1990)), however, LBP at high concentration has been shown to detoxify LPS in vitro and in vivo (Lamping et al., J. Clin. Invest. 101, 2065-2071 (1998)). However, human subjects suffering from disorders involving

bacteria and their endotoxin have been shown to exhibit substantially elevated levels of LBP circulation (at concentrations of 50-100 μg/ml of serum), yet these high circulating levels of LBP do not appear to have inhibited the adverse effects of bacterial endotoxin in circulation that were experienced by these subjects (Dedrick et al., US Patent 5,990,082, column 4). Since the role of LBP in promoting or alleviating adverse effects of endotoxin in circulation remains unclear, the experimentation of using LBP to treat endotoxin related disorder is needed for various in vitro and in vivo studies.

The specification describes briefly on the cloning of LBP (see page 3, lines 23+), however the instructions on how to construct the LBP expression plasmid/vector and to express LBP from the clone in cells are not described. It does not appear that the ordinary artisan can reproduce LBP in cell lines. If the cell lines are unique and can not be produced by routine methods, deposit is required. If the deposit has been made under the terms of the Budapest Treaty, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the cell line has been deposited under the Budapest Treaty and that the cell line will be irrevocably and without restriction or condition be released to the public upon the issuance of a patent would satisfy the deposit requirement made herein. See 37 CFR 1.808. Further, the record must be clear that the deposit will be maintained in a public depository for a period of 30 years after the date of deposit or 5 years after the last request for a sample or for the enforceable life of the patent, whichever is longer. See 37 CFR 1.806. If the deposit has not been made under the Budapest treaty, then an affidavit or declaration by applicants or someone

associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth in 37 CFR 1.801-1.809, have been met. Amendment of the specification to disclose the date of deposit and the complete name and address of the depository is required. If the deposit was made after the effective filing date of the application for a patent in the United States, a verified statement is required from a person in a position to corroborate that the plasmid described in the specification as filed are the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed. Applicant's attention is directed to *In re Lundak*, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985), and 37 CFR 1.801-1.809 for further information concerning deposit practice.

The specification does not describe any of variants, mutants and hybrid proteins of LBP nor discloses how to obtain these variants, mutants and hybrid proteins of LBP such that one skilled in the art would have been able to reproduce same from the instant application. Certain claims, e.g., claim 16 recite the hybrid protein of LBP with the LPS binding site of BPI or with LPS binding site of the LALF, however the binding site(s) of LPS for these proteins are not described so as to one skilled in the art be able to reproduce same from the instant application. Claim 17 also recites LBP variants with certain amino acids being exchanged, but none are described in the specification per se, such as by position or type. It is not apparent which of the amino acids that can be substituted at position 91-101 would result in improved LPS binding.

The application does not define any substitution that would have been expected to improve binding and there is no reference sequence identifier or sequence identified in the application as a reference for the numbering scheme recited in claim 17. Since it is not routine in the art to engage in *de novo* experimentation where the expectation of success is unpredictable, the skilled artisan would require additional guidance in order to make and use such compounds. Without such guidance, the experimentation left to those skilled in the art is undue.

The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the scope of the claims, the nature of the invention, the state of the prior art, the absence of working examples, the unpredictability of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 12-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite because of the use of the term "its variants, mutants or hybrid proteins". The term "its variants, mutants or hybrid proteins" renders the claim indefinite, it is not clear what kind of variants, mutants or hybrid proteins are, e.g., what kind of modification is made on the LBP or what is the other partner for the hybrid protein of LBP. It is also not clear whether the variants, mutants or hybrid proteins have the same properties of the complete LBP. Claims 13-15 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

3. Claims 16 and 17 are indefinite because of the use of the term "LPS". The term "LPS" render the claim indefinite, it is unclear what LPS is. "LPS" should be preceded by the full spelled out words.

4. Claim 17 is indefinite because of the use of the term "by individual exchanges of amino acids". The term "by individual exchanges of amino acids" render the claim indefinite, it is unclear what kind of changes have been made at amino acids 91-101, e.g., is it a conservative substitution or how many substitutions have been made at the LPS binding site for which no reference SEQ ID NO: is set forth.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claim 12 is rejected under 35 U.S.C. 102(b) as being anticipated by Gazzano-Santoro *et al.* (Infection and Immunity 62, 1185-1191 (1994)).

Gazzano-Santoro *et al.* teach both a recombinant fragment ($rBPI_{23}$) of a bactericidal/permeability-increasing protein (BPI) and human recombinant LBP (rLBP) can bind lipid A and Escherichia coli J5 bacteria, respectively, and $rBPI_{23}$ has a higher binding affinity toward endotoxin than rLBP (abstract; page 1187, right column; Figures 1, 2 and 3). In the presence of rLBP, $rBPI_{23}$ can effectively block the proinflammatory response of peripheral blood mononuclear cells to endotoxin (abstract; page 1188, right column; Figure 4). Therefore, LBP either alone or combined with $rBPI_{23}$ is used as active component of an agent which anticipates

claim 12. The phrase "for the treatment of septicemia" is an intended use, it does not play any weight on the claimed invention.

6. Claims 12, 16 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Scott *et al.* (WO 94/25476).

Scott *et al.* teach a pharmaceutical composition comprises a therapeutically effective amount of a BPI variant, a LBP variant, or an LBP-BPI chimera and a pharmaceutically acceptable carrier which can be used to treat endotoxin-related disorder (pages 13, 14, 18, 22, 23, 25; Tables 3-6). The composition containing LBP variant such as $L_{(S77->K)(R86->K)\ (S96->K)\ (L118->K)(R126->K)}$ (NCY141 in Table 3) which has a mutation at position 96 meets the criteria of claims 12 and 17, and LBP-BPI chimera such as $L_{197(I43->V)}B_{200-456(N206->D)}$ (NCY 103 in Table 3) which is a hybrid protein of LBP (L) and BPI (B) meets the criteria of claims 12 and 16.

7. Claims 12 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Heavner *et al.* (WO 95/08560).

Heavner *et al.* teach pharmaceutical compositions comprise peptides derived from portions of the sequences of amino acids 95-104 of LBP such as Arg-Lys-Ser-Phe-Phe-Lys-Leu-GlN-Gly-Ser-Phe-Asp-Val-Ser-Val-NH_2 (SEQ ID NO:1) and its variants (SEQ ID NO:2-64, see pages 9-12, 21-22 and Examples 1-9) which meets the criteria of claims 12 and 17.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

8. Claims 12, 13, 16 and 17 are rejected under 35 U.S.C. 102(a) as being anticipated by Lamping *et al.* (Immune Consequences Trauma, Shock Sepsis, Int. Congr. 4 th, pages 15-19 (March 1997)).

Lamping *et al.* teach the inhibition of LBP-LPS interaction by human recombinant LBP (meets criteria of claims12 and 13), LBP-peptides with mutation at amino acid position 94 and 95 (meets claim 17 criteria), and chimeric mutants such as LBP-BPI and LBP-LALF (meets claim 17 criteria, see whole document).

Conclusion

9. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, Ph. D. can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D.
Patent Examiner

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June 12, 2001

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